의학석사 학위논문

Clinical Usefulness of AJCC Response Criteria in Breast Cancer Patients Who Treated with Long Course Neoadjuvant Chemotherapy

6주기 이상 장기간 선행항암요법을 받은 유방암 환자에서 American Joint Committee on Cancer (AJCC) 반응평가 기준의 임상적 유용성

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A thesis of the Degree of Master

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Clinical Usefulness of AJCC Response Criteria in Breast Cancer Patients Who Treated with Long Course Neoadjuvant Chemotherapy

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Abstract

Introduction

Neoadjuvant chemotherapy (NAC) is the standard therapy for American Joint Committee on Cancer (AJCC) stage II or III breast cancer, currently. AJCC response criteria for NAC is a known useful tool for evaluating response to NAC as well as predicting survival in short course NAC. The purpose of this study is to evaluate the clinical usefulness of AJCC response criteria in long course (≥6 cycles) NAC. We also analyzed prognostic clinicopathological factors for relapse free survival (RFS) in four breast cancer subtypes.

Method

From January 2009 to December 2010, a total of 183 consecutive stage II or III breast cancer patients who received NAC of 6 cycles or more were enrolled in this study. AJCC response after NAC and the clinicopathological factors of these patients were reviewed retrospectively. AJCC response criteria were as follows: (1) complete response (CR) - absence of invasive carcinoma in the breast and node; (2) partial response (PR) - decrease in either or both T or N stage; (3) no response (NR) - no change or increase in either or both T or N stage.

Result

Median follow up period of 183 patients was 38.0 months. Among them, CR, PR, and NR by AJCC criteria were 22 (12.0%), 123 (67.2%), and 38 (20.8%) respectively. The 3-year RFS rates were 90.9% in CR, 80.8% in PR, and 48.5% in NR. AJCC response was significantly associated with relapse free survival (RFS) ($P<0.001$). After adjusting potential prognostic factors, AJCC response was independently associated with RFS (P=0.004).

Conclusion

AJCC response criteria is a useful clinical predictor for RFS in long course NAC as for in short course NAC in stage II/III breast cancer.

Keywords

Stage II or III breast cancer, neoadjuvant chemotherapy, AJCC response, relapse free survival

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Introduction

Breast cancer is the most common cancer in women worldwide and annually 1.38 million cases are newly diagnosed. [1] It is the second most common cancer in female in Korea, and 16,396 new patients were diagnosed during 2010. [2] [3] About 44% of the newly diagnosed breast cancer patients are initially stage II or III, [4] and neoadjuvant chemotherapy (NAC) or primary systemic therapy has become a standard treatment for these population. [5] Response to NAC has thought to be useful in prognostic and predictive aspects. Pathologic complete response (pCR) is known to be the most important prognostic factor and the useful surrogate marker for overall survival in NAC setting. [6-8] Despite its clinical usefulness, discrimination into pCR and non-pCR is too simple because non-pCR includes broad range of actual responses (from partial response to even progressive disease). Several groups had proposed new methods for grouping post-NAC patients to evaluate the response to NAC. [9-12] In 2010, American Joint Committee on Cancer (AJCC) 7^{th} edition proposed the new response criteria for NAC. [13] Keam et al. validated AJCC response criteria for NAC in 398 patients who received 3 cycles of doxorubicin plus docetaxel chemotherapy, and AJCC response criteria seemed to be useful in evaluating response of NAC, as well as in predicting survival in short course of NAC. [14] Since the

middle of last decade, importance of pCR achievement is emphasized and to obtain the higher rate of pCR, extended cycles of neoadjuvant chemotherapy was introduced. [15-17] Recently, six to eight cycles of NAC has become the standard treatment in practice.

In this study, we evaluated and validated AJCC response criteria in long course (≥6 cycles) of NAC. In addition, we evaluated the clinical usefulness and prognostic value of AJCC response criteria in four different breast cancer groups, [18] described precisely later in this paper. We also analyzed prognostic value of clinical factors and biomarkers for relapse free survival (RFS) in these four breast cancer subtypes.

Materials and Methods

Study Population and Treatment

Between January 2009 and December 2010, a total of 249 stage II/III breast cancer patients who received NAC were screened. Sixty-six patients were excluded because of received less than 6 cycles of NAC. Finally 183 patients were enrolled in this study.

Detailed eligibility criteria is as followed : 1) pathologically confirmed breast cancer by core needle biopsy, 2) clinical stage II or III, 3) presence of objective measurable lesion by Response Evaluation Criteria In Solid

Tumors (RECIST) version 1.1, [19] 4) Eastern Cooperative Oncology Group (ECOG) performance status 0-2, [20] 5) previously untreated, 6) cycles of neoadjuvant chemotherapy of 6 or more. Initial evaluation included physical examination, mammography, breast ultrasonography, computed tomography of chest, bone scan, and breast magnetic resonance imaging (MRI). Initial tumor size was measured by MRI. Initial nodal staging was done by physical examination and by computed tomography (CT). After completed 6 or more cycles of neoadjuvant chemotherapy before definitive surgery, the patients were re-examined for response evaluation. Thereafter, the patients received curative surgery followed by adjuvant chemotherapy by physician's decision considering response to NAC and final pathologic stage. [21] Patients received additional adjuvant radiation therapy, [22-25] trastuzumab [26, 27] and hormonal therapy, [28-31] if indicated.

The study protocol was reviewed and approved by the institutional review board at the Seoul National University Hospital. Recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

Response Evaluation

For evaluation of radiologic response, we obtained ultrasonography and MRI

for primary breast cancer and chest CT for lymph node evaluation before and after NAC. The radiologic response was evaluated with RECIST criteria version 1.1. [19] The initial clinical and post-NAC pathologic staging were done based on the AJCC 7th edition, and the details of AJCC response criteria for NAC were as followed. [32]

(1) Complete response (CR) is defined as the absence of invasive carcinoma in the breast and lymph nodes. Residual in situ cancer, in the absence of invasive disease, constitutes a CR. Patients with isolated tumor foci in lymph nodes are not classified as having a CR.

(2) Partial response (PR) is defined as a decrease in either or both T or N stage compared to the pretreatment T or N, and no increase in either T or N. After chemotherapy, one should use the method that most clearly defined tumor dimensions at the baseline for this comparison, although prechemotherapy pT cannot be measured.

(3) No response (NR) is defined as no apparent change in either the T or N categories compared to the clinical pretreatment assignments, or increase in either the T or N categories at the time of y pathologic evaluation.

Pathologic complete response (pCR) is defined as complete disappearance of invasive carcinoma, in both the breast and the axillary lymph nodes, after NAC. Residual ductal carcinoma in situ (DCIS) was included in the pCR.

Clinicopathological Examination

The clinical characteristics (age at diagnosis, date of diagnosis, date, cycles and regimen of neoadjuvant chemotherapy, date of surgery, adjuvant therapy, date of last visit, date of relapse) and the laboratory test results (Follicle stimulating hormone (FSH), Luteinizing hormone (LH) and estradiol levels at diagnosis for determine menopausal status [33-36]) were obtained by retrospective review of electronic medical record system. We performed an immunohistochemistry (IHC) using tissues obtained before and after NAC. Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), p53, bcl-2, epidermal growth factor receptor (EGFR) and Ki-67 expressions were evaluated. Cytokeratin 5/6 (CK5/6) were also evaluated in post-NAC surgical specimen. IHC was performed as previously described in our center's study series. [37-40] In case of HER2 IHC 2+, fluorescent in situ hybridization (FISH) was performed to determine HER2 positivity. Positivity thresholds for classification were ER ≥ 1%; PR ≥ 1%; HER2 = IHC 3+ (>10% invasive tumor cells with intense and circumferential membrane staining) and/or FISH positive (HER2:CEP17 ratio ≥ 2.2), [41, 42] and p53 ≥ 25%. [43-45] The Ki-67 threshold of high ≥14% was based on work by Cheang et al., in which 14% best discriminated between luminal-A and B tumors. [46]

Breast Cancer Subtypes

Breast cancer is further classified into several groups according to their molecular alteration, cellular composition and clinical outcome. Tumor classification is useful in determining and predicting response to treatment as well as providing prognostic information. In this study, we classified breast cancer patients into four subgroups, luminal A (LA), luminal B (LB), HER2 enriched (HER2) and triple negative breast cancer (TNBC) group, definition adopted by the 2011 St Gallen Consensus Panel. [18, 47] Definitions of each subgroup are as followed,

(1) Luminal A (LA) : (highly endocrine responsive) : ER positive, PR positive, HER2 negative and Ki-67 low. The few ER-negative/PR-positive cases were considered ER-positive/PR-positive.

(2) Luminal B (LB) : (moderately endocrine responsive) : ER positive and PR negative independent of other parameters, or ER positive, PR positive and at least one of grade 3, HER2 positive and/or Ki-67 high

(3) HER2 enriched (HER2) : ER negative, PR negative and HER2 positive

(4) Triple negative breast cancer (TNBC) : ER negative, PR negative and HER2 negative regardless of the expression of EGFR and basal cytokeratins.

Statistical Analysis

Relapse-free survival (RFS) was determined as the interval between the initiation of neoadjuvant chemotherapy and the date when disease relapse or progression was first documented, or the date of death from any cause. Local, regional, and distant relapse were all included in the disease relapse, and the contralateral breast cancer was not regarded as relapse. The Kaplan- Meier product limit method and the Cox proportional hazard regression (PHR) model were used for survival analyses. The log-rank tests were used to compare RFS between different groups. Hazard function is the instantaneous failure rate at time t, which is the probability of event in the next small interval. Differences between breast cancer subtypes with regard to clinicopathologic characteristics were examined using 1-way analysis of variance (ANOVA) for the continuous variables (age, pre- and post NAC tumor size, follow-up duration and relapse free survival) and χ^2 tests for the remaining. All statistical tests were two-sided, with the level of significance established at $P < 0.05$. All the statistical analyses were carried out in SPSS version 21.0 (SPSS, Inc., Chicago, IL)

Results

Patients and Treatment

A total of 183 patients with median age of 46 (range from 25 to 71 years) were evaluated in this study and the median follow up duration was 38.0 months (range from 9 to 53 months). At the data cut-off (June 2013), 40 patients (21.9%) developed recurrent disease. The median RFS was not reached at the time. The baseline characteristics of 183 patients are described in Table 1. Thirty patients (16.4%) were initially stage II and 153 (83.6%) were stage III. The median of initial tumor size in the greatest dimension by breast MRI, chest CT or breast sonography was 47mm (range from 0 to 143mm). The median post-NAC tumor size by image was 24mm (range from 0 to 112mm) and the size by pathologic review was 15mm (range from 0 to 121mm). One hundred and eleven (60.6%) were hormone receptor positive and 61 (33.3%) were HER2 positive. NAC regimens were heterogenous in comparison with our previous study. [14] Majority of the patients received both anthracycline and taxane containing NAC. One hundred and twenty-eight (69.9%) received concurrent anthracycline and taxane regimen and 47 (25.7%) received sequential anthracycline and taxane regimen. Ten patients (5.5% of total patients and 16.4% of HER2 positive patients) received HER2 targeted agent (trastuzumab or T-DM1) containing regimen.

Table 1. Baseline Characteristics

Variables	Number of patients	
	No	%
Total population	**183**	
Age, median (range)	**46 (25-71)**	
Histology		
Invasive ductal carcinoma	**167**	**91.3**
Others	**16**	**8.7**
Premenopause	**109**	**59.6**
Post-menopause	**74**	**40.4**
Tumor size, pre-neoadjuvant chemotherapy median(mm) (range)	**47 (0-143)**	
Tumor size, post-neoadjuvant chemotherapy		
Clinical(mm), median(range)	**24 (0-112)**	
Surgical specimen(mm), median(range)	**15 (0-121)**	
Regimen of Neoadjuvant Chemotherapy		
Concurrent anthracycline+taxane	**128**	**69.9**
Sequential anthracycline+taxane	**47**	**25.7**
HER-2 directed therapy containing regimen	**10**	**5.5**
Others	**1**	**0.5**
Type of Surgery		
Breast conserving surgery	**104**	**56.8**
Mastectomy	**79**	**43.2**
Initial Clinical Stage		
IIA	**3**	**1.6**
IIB	**27**	**14.8**
IIIA	**94**	**51.4**
IIIB	**26**	**14.2**
IIIC	**33**	**18.0**
Hormone receptor and HER-2[a] expression status		
Hormone receptor	**111**	**60.6**
Estrogen receptor	**103**	**56.3**
Progesterone receptor	**68**	**37.1**
HER2	**61**	**33.3**

Pathologic subtype			
Luminal A		**41**	**22.4**
Luminal B		**85**	**35.5**
HER2 negative		**35**	**19.1**
HER2 positive		**30**	**16.4**
HER2		**31**	**16.9**
TNBC[b]		**46**	**25.1**
Ki-67			
Pre-neoadjuvant chemotherapy	**Low (<14%)**	**99**	**59.3**
	High (≥14%)	**68**	**40.7**
Post-neoadjuvant chemotherapy	**Low (<14%)**	**123**	**81.5**
	High (≥14%)	**28**	**18.5**
Pathologic Stage			
yp0		**22**	**12.0**
ypIA		**41**	**22.4**
ypIIA		**42**	**23.0**
ypIIB		**22**	**12.0**
ypIIIA		**38**	**20.8**
ypIIIB		**2**	**1.1**
ypIIIC		**16**	**8.7**
Adjuvant therapy			
Trastuzumab		**55**	**30.1 (90.2% of HER2 positive patients)**
Hormonal therapy		**103**	**56.6 (92.8% of HR positive patients)**
Radiation therapy		**158**	**86.3**
Chemotherapy		**62**	**33.9**

a HER2 : human epidermal growth factor receptor 2
b TNBC : triple negative breast cancer

Response to the Neoadjuvant Chremotherapy

Response to the neoadjuvant chemotherapy (NAC) was evaluated in two methods. Table 2 showed the results by AJCC response criteria. Among 183 patients pCR, PR and NR were 22 (12.0%), 123 (67.2%) and 38 (20.8%) respectively. Of all the patients, pre- and post-NAC image were available. Results from radiologic response by RECIST v1.1 were shown in Table 3. CR, PR, SD and PD were 17 (9.3%), 115 (62.8%), 43 (23.5%) and 8 (4.4%) respectively.

Among 17 patients showed CR by RECIST criteria, 6 (35.3%) were also had pCR by AJCC criteria. And among 115 patients showed PR by RECIST criteria, 82 (71.3%) were had PR by AJCC criteria. AJCC response criteria and RECIST v1.1 had statistically significant correlation (P <0.001). (Table 4)

Table 2. AJCC Response after Neoadjuvant Chemotherapy

AJCC Response	Number of patients	
	No	%
pCR[a]	**22**	**12.0**
PR[b]	**123**	**67.2**
NR[c]	**38**	**20.8**

a pCR: pathologic complete response , b PR: partial response , c NR: no response

Table 3. Radiological response after Neoadjuvant Chemotherapy

Radiologic Response (RECIST v1.1[a])	Study population	
	Number	Percent (%)
CR	17	9.3
PR	115	62.8
SD	43	23.5
PD	8	4.4
Total	183	100

a RECIST v1.1 : Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
b CR : complete reponse , c PR : partial response, d SD : stable disease, e PD : progressive disease

Table 4. Relation between Radiological Response Criteria and AJCC Response Criteria

Radiologic Response (RECIST v1.1[a])	AJCC response[b]			*P*
	pCR[g]	PR[h]	NR[i]	
CR[c]	6 (35.3%)	10 (58.8%)	1 (5.9%)	< 0.001
PR[d]	15 (13.0%)	82 (71.3%)	18 (15.7%)	
SD[e]	1 (2.3%)	25 (58.1%)	17 (39.5%)	
PD[f]	0 (0%)	6 (75%)	2 (25%)	

a RECIST v1.1 : Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
b AJCC : American Joint Committee on Cancer (AJCC), 7th edition
c CR : complete reponse, d PR : partial response, e SD : stable disease, f PD : progressive disease, g pCR: pathologic complete response, h PR: partial response, i NR: no response

We compared the short course (<6 cycles) and the long course (≥6 cycles) NAC and response to the NAC by both radiologic criteria and the AJCC criteria, during the study period. Sixty-six patients received less than 6 cycles of NAC. As shown in Table 5, CR+PR rate by RECIST were significantly higher in long course NAC group. (50% vs 72.1%, *P*=0.008) Pathologic CR by AJCC criteria was also significantly higher in long course NAC group. (1.5% vs 12.0%, *P*=0.027)

Table 5. Radiological Response and AJCC[b] Response in Short Course and Long Course Neoadjuvant Chemotherapy Patients

	Neoadjuvant chemotherapy cycle				
	< 6 cycles		≥6 cycles		P value
	Number	%	Number	%	
Radiologic Response (RECIST v1.1[a])					***0.008***
CR	**3**	**4.5%**	**17**	**9.3%**	
PR	**30**	**45.5%**	**115**	**62.8%**	
SD	**30**	**45.5%**	**43**	**23.5%**	
PD	**3**	**4.5%**	**8**	**4.4%**	
AJCC Response[b]					***0.027***
pCR	**1**	**1.5%**	**22**	**12.0%**	
PR	**46**	**69.7%**	**123**	**67.2%**	
NR	**19**	**28.8%**	**38**	**20.8%**	

a RECIST v1.1 : Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1
b AJCC : American Joint Committee on Cancer (AJCC), 7th edition

Correlation between AJCC Response and other Clinicopathological Factors for Relapse Free Survival

Table 2 showed the result of response by AJCC criteria for NAC. The 3-year RFS rates were 90.9% in CR, 80.8% in PR, and 48.5% in NR group (Figure 1, log-rank, $P<0.001$). AJCC response was significantly associated with relapse free survival (RFS) (hazard ratio 0.309, 95% confidence interval (CI) 0.172-0.556, $P<0.001$). Figure 2 showed relapse rate (percent) at the specific time from surgery (months) according to the AJCC response. About 30% of NR group patients relapsed within 1 year and the peak time of relapse was 2 years. On the contrary, CR and PR group showed similar time course of relapse with the peak rate at 3-4 years.

After adjusting potential prognostic factors, AJCC response was independently associated with RFS ($P=0.004$). But the pathologic complete response was not statistically significant predictor of RFS (Figure 3, log-rank, $P=0.120$), despite the curve showed the survival difference between two groups.

Figure 1 AJCC Response and Relapse Free Survival

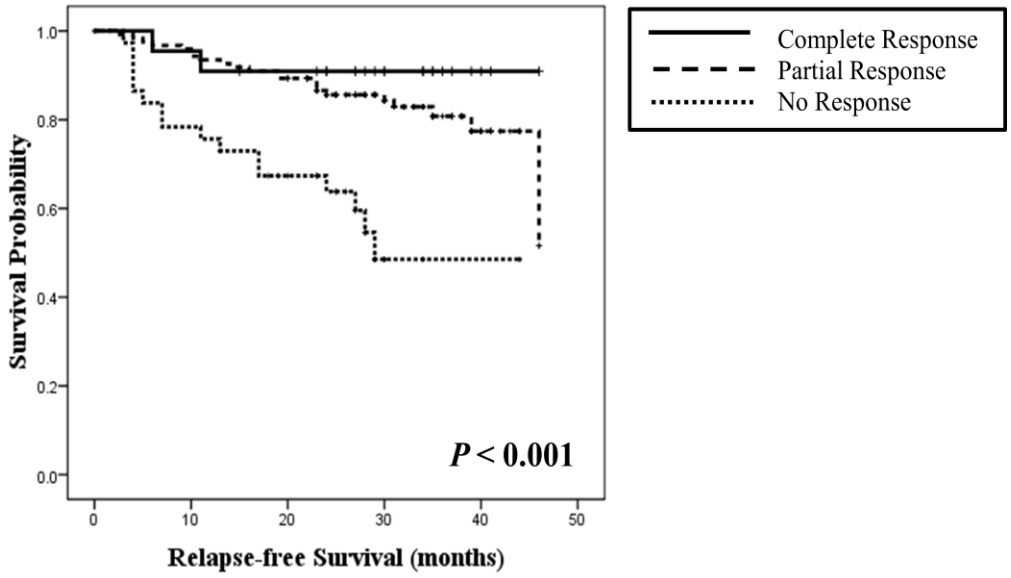


Figure 2 Relapse Rate and Time from Surgery according to AJCC Response Criteria

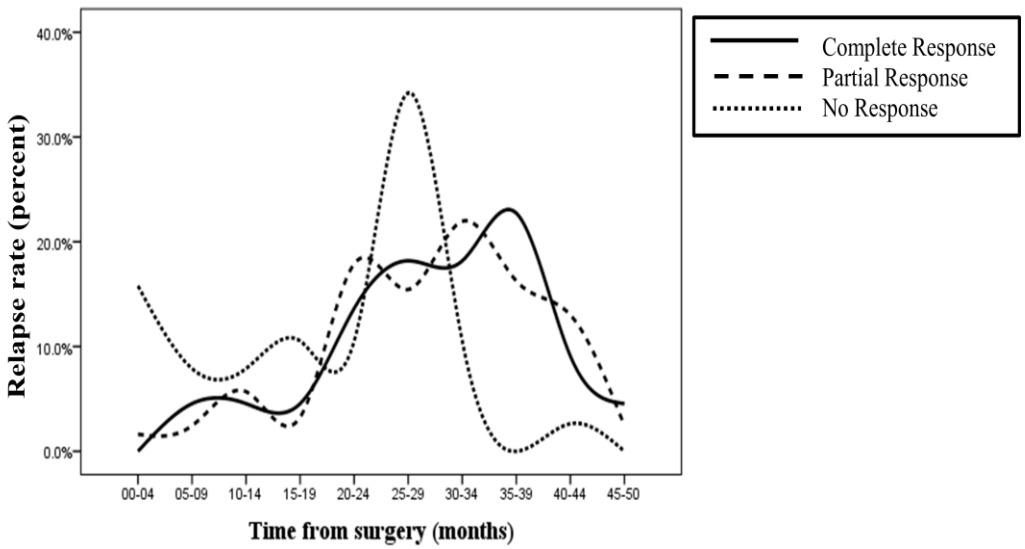
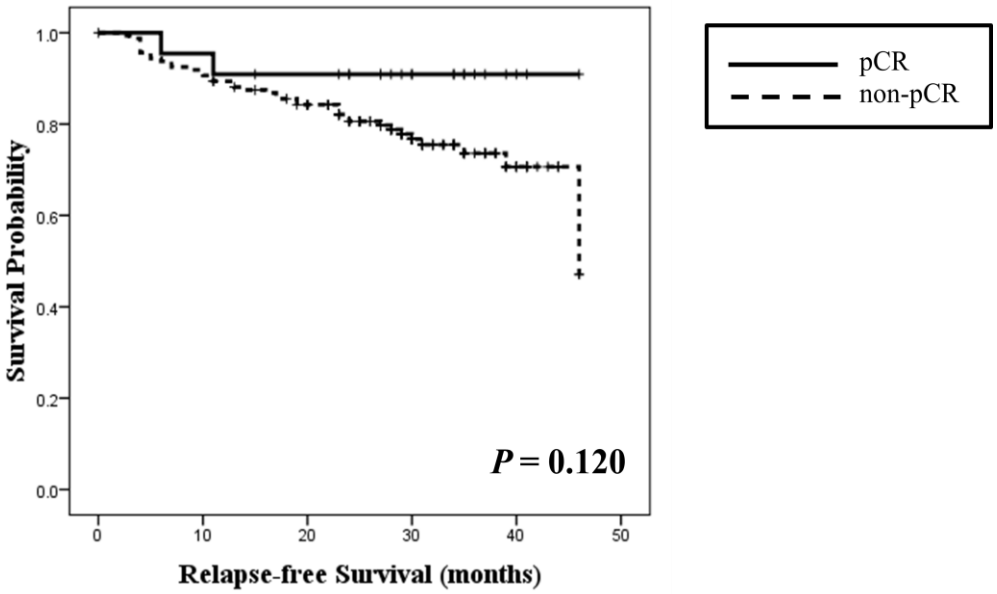
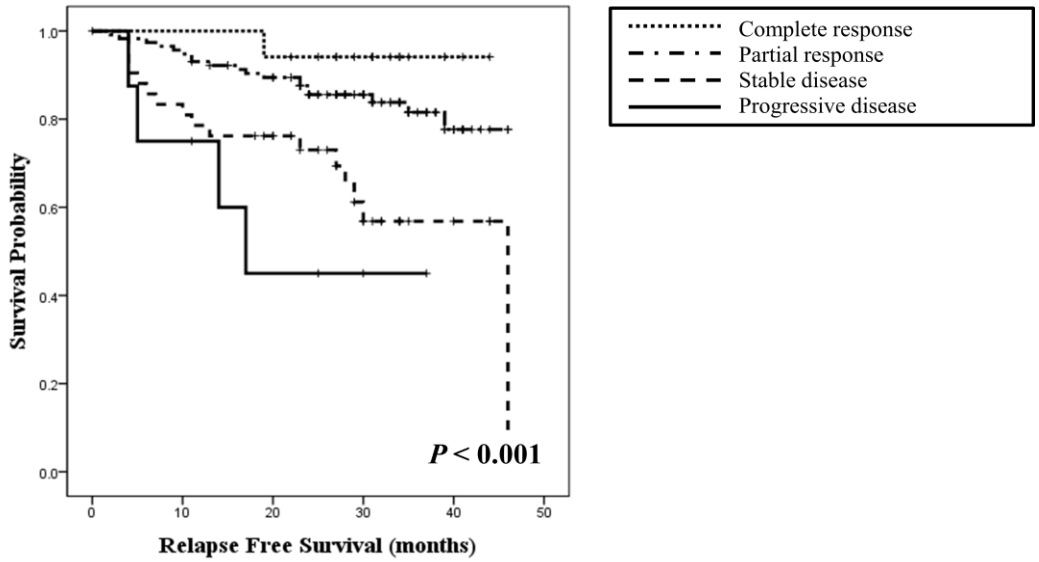


Figure 3 Pathologic Complete Response and Relapse Free Survival



As we already described in previous section, radiologic response criteria and the AJCC criteria correlated well significantly. And the radiologic responses were also associated with relapse free survival (RFS). (Figure 4, log-rank, *P<0.001*)

Figure 4. Radiologic response and Relapse Free Survival



We performed the univariate and the multivariate Cox proportional hazard regression analysis between clinicopathologic variables and survival (Table 6). The pathologic stage (stage I vs II, III, IV), type of surgery (breast conserving surgery vs mastectomy), breast cancer subtype (luminal A vs others) and hormone receptor positivity (HR positive vs negative) were significantly associated with RFS both in univariate and multivariate analyses. But the HER2 positivity (P=0.734), both initial and final pathological Ki-67 expression index (P=0.236 and P=0.182 respectively) and triple negativity (ER, PR and HER2 negative, P=0.919) were not significantly associated with RFS. Post-treatment biomarker analyses in all patients showed that ER, PR and Bcl-2 positivity is positively associated with RFS with statistical significance (Table 7, P=0.019, P=0.010 and P=0.029 respectively) but lost statistical power after multivariate analysis (P=0.602, P=0.114 and P=0.196 respectively).

Table 6. Univariate & Multivariate Analysis for Relapse Free Survival in All Patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
≤46	0.685	0.364-1.287	*0.240*		-	
>46	1					
Menopausal status						
Premenopause	0.846	0.449-1.594	*0.605*		-	
Postmenopause	1					
pCR[a]	0.342	0.082-1.420	*0.140*		-	
vs on-pCR	1					
AJCC response						
CR	0.309	0.172-0.556	*0.000*	0.374	0.192-0.728	*0.004*
PR[b] & NR[c]	1			1		
Surgery						
BCS[d]	0.428	0.228-0.803	*0.008*	0.475	0.252-0.894	*0.021*
mastectomy	1			1		
Pathologic Stage						
yp0,I	0.235	0.092-0.600	*0.002*	0.267	0.094-0.756	*0.013*
ypII, III, IV	1			1		
Hormone receptor						
Positive	0.447	0.236-0.846	*0.013*	0.402	0.198-0.818	*0.012*
negative	1			1		
HER2[e]					-	
Positive	1.059	0.761-1.474	*0.734*			
negative	1					
TNBC[f]	1.038	0.056-2.131	*0.919*		-	
vs non-TNBC	1					
Subtype						
Others	2.641	1.015-6.877	*0.047*	3.180	1.039-9.727	*0.043*
Luminal A	1			1		

Ki-67 pre-neoadjuvant chemotherapy				-
High (≥14%)	**1.120**	**0.929-1.351**	***0.236***	
Low (<14%)	**1**			
Ki-67 post-neoadjuvant chemotherapy				-
High (≥14%)	**1.676**	**0.785-3.579**	***0.182***	
Low (<14%)	**1**			

a pCR: pathologic complete response
b PR: partial response
c NR: no response
d BCS : breast conserving surgery
e HER2 : human epidermal growth factor receptor 2
f TNBC : triple negative breast cancer

Table 7. Post-treatment Prognostic Biomarkers for Relapse

Variables		In all Patients			HR positive patients			TNBC		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Ki-67										
Pre-NAC[a]	**High**	**0.893**	**0.740-1.077**	***0.236***	**0.932**	**0.752-1.156**	***0.523***	**1.129**	**0.571-2.273**	***0.726***
	Low	**1**			**1**			**1**		
Post-NAC[a]	**High**	**1.676**	**0.785-3.579**	***0.182***	**1.310**	**0.299-5.744**	***0.721***	**2.828**	**0.754-10.607**	***0.123***
	Low	**1**			**1**			**1**		
Ki-67 change										
High→Low		**3.580**	**0.458-27.984**	***0.224***	**2.434**	**0.267-22.207**	***0.430***	**0.180**	**0.035-0.935**	***0.041***
others		**1**			**1**			**1**		
Δ Ki-67[b]		**0.990**	**0.975-1.005**	***0.194***	**1.001**	**0.970-1.032**	***0.969***	**0.986**	**0.961-1.012**	***0.300***
ER[c]										
Positive		**0.467**	**0.246-0.884**	***0.019***		**-**			**-**	
Negative		**1**								
PR[d]										
Positive		**0.358**	**0.164-0.779**	***0.010***		**-**			**-**	
Negative		**1**								
p53										
High		**1.160**	**0.845-1.592**	***0.358***	**0.942**	**0.591-1.499**	***0.799***	**1.259**	**0.640-2.475**	***0.505***
Low		**1**			**1**			**1**		
Bcl2										
Positive		**0.496**	**0.264-0.932**	***0.029***	**1.026**	**0.550-1.916**	***0.936***	**0.468**	**0.132-1.664**	***0.241***
Negative		**1**			**1**			**1**		
EGFR										
Positive		**0.944**	**0.490-1.645**	***0.957***	**0.502**	**0.183-1.739**	***0.182***	**0.238**	**0.036-2.237**	***0.231***
Negative		**1**			**1**			**1**		
HER2										
Positive		**1.059**	**0.761-1.474**	***0.734***	**1.304**	**0.428-3.984**	***0.641***		**-**	
Negative		**1**			**1**					
CK5/6										
Positive		**1.090**	***0.554-2.416***	***0.803***	**1.067**	**0.307-3.704**	***0.919***	**0.704**	**0.199-2.494**	***0.587***
Negative		**1**			**1**					

a NAC : neoadjuvant chemotherapy

b Δ Ki-67 : (post-neoadjuvant chemotherapy Ki-67) - (pre-neoadjuvant chemotherapy Ki-67) as continuous variable

c ER : estrogen receptor

d PR : progesterone receptor

Breast Cancer Subtypes and Clinicopathological Factors for Relapse Free Survival

We divided the patients into four subgroups (luminal A, luminal B, HER2, and triple-negative) as previously described. The baseline demographic features of each group were shown in Table 8-1. Premenopausal patients were larger in number in luminal A group than others. Initial tumor size is smaller in TNBC group than others. Rate of pCR is higher in TNBC and HER2 group and the rate of AJCC response CR plus PR is also higher in TNBC and HER2 groups. Figure 5-1 showed difference in RFS among the subgroups. Luminal A and HER2 positive luminal B showed longer RFS and HER2 group showed worst result in RFS (log rank, P=0.004). Figure 5-2 showed relapse rate (percent) at the specific time from surgery (months) in each groups. In HER2 enriched group, about 30% of patients relapsed during the first year, in other words during adjuvant trastuzumab and/or chemotherapy or radiotherapy. The other groups showed peak rate of relapse at the two to three years from surgery.

Table 8. Subgroups Analysis

1) Demographic features

Variables	Number of patients										
	Luminal A		Luminal B				HER2[j]		TNBC[k]		*P*
			HER2[j] (-)		HER2[j] (+)						
	No	%	No	%	No	%	No	%	No	%	
Number	41	100	35	100	30	100	31	100	46	100	
Age, median (range)	44 (30-60)		49 (25-67)		49 (30-71)		47 (31-66)		45 (26-65)		*0.230*
Menopausal status											*0.135*
Premenopause	30	73.2	20	57.1	13	43.3	20	64.5	26	59.6	
Post-menopause	11	26.8	15	42.9	17	56.7	11	35.5	20	43.5	
Histology											*0.061*
Invasive ductal carcinoma	35	85.4	30	85.7	27	90.0	29	93.5	46	100	
Others	6	14.6	5	24.3	3	10.0	2	6.5	0	0	
Tumor size(mm), Pre-NAC[a] Median (range)	47 (5-143)		54 (0-130)		45.0 (16-110)		59.0 (16-130)		40.5 (10-110)		*0.199*
Tumor size(mm), Post-NAC[a]											
Clinical median(range)	29 (8-102)		24 (0-64)		27.5 (0-112)		20.0 (0-100)		17.0 (0-110)		*0.298*
Pathology median(range)	27 (0-95)		30 (0-121)		10.5 (0-106)		8.0 (0-100)		4.0 (0-85)		*0.000*
Clinical Stage											*0.312*
IIA	0	0	0	0	0	0	0	0	3	6.5	
IIB	7	17.1	5	14.3	6	20.0	3	9.7	6	13.0	
IIIA	23	56.1	17	48.6	16	53.3	15	48.4	23	50.0	
IIIB	5	12.2	7	20.0	1	3.3	8	25.8	5	10.9	
IIIC	6	14.6	6	17.1	7	23.3	5	16.1	9	19.6	
NAC[a] regimen											*0.002*
Concurrent A/T[b]	24	58.5	29	82.9	18	60.0	20	64.5	36	78.3	
Sequential A→T[c]	17	41.5	6	17.1	5	16.7	7	22.6	10	21.7	
HER2 directed [d]	0	0	0	0	6	20.0	4	12.9	0	0	
Others[e]	0	0	0	0	1	3.3	0	0	0	0	
Type of Surgery											*0.297*
BCS[f]	21	51.2	20	57.2	17	56.7	14	45.2	32	69.6	
Mastectomy	20	48.8	15	42.9	13	43.3	17	54.8	14	30.4	

Ki-67												
Pre-	Low	33	19.8	17	10.2	18	10.8	14	8.4	17	10.2	*0.000*
NAC[a]	High	0	0	16	9.6	11	6.6	13	7.9	28	16.8	
Post-	Low	41	27.2	28	18.5	15	9.9	19	12.6	20	13.2	*0.000*
NAC[a]	High	0	0	1	0.7	9	6.0	5	3.3	13	8.6	
pCR		0	0	4	11.4	4	13.3	5	16.1	9	19.6	*0.071*
AJCC response												*0.122*
pCR[g]		0	0	4	11.4	4	13.3	5	16.1	9	19.6	
PR[h]		29	70.7	21	60.0	22	73.4	22	71.0	29	63.0	
NR[i]		12	29.3	10	28.6	4	13.3	4	12.9	8	17.4	
Pathologic Stage												*0.001*
yp0		0	0	4	11.4	4	13.3	5	16.1	9	19.6	
ypIA		3	7.3	6	17.1	8	26.7	9	29.0	15	32.6	
ypIIA		9	22.0	7	20.0	8	26.7	7	22.6	11	23.8	
ypIIB		9	22.0	7	20.0	4	13.3	1	3.2	1	2.2	
ypIIIA		18	43.9	9	25.7	2	6.7	4	12.9	5	10.9	
ypIIIB		0	0	1	2.9	0	0	1	3.2	0	0	
ypIIIC		2	4.9	1	2.9	4	13.3	4	12.9	5	10.9	
Adjuvant therapy												
Trastuzumab		0	0	2	5.7	24	80.0	29	93.5	0	0	
Hormonal therapy		41	100	30	85.7	25	83.3	4	12.9	3	6.5	
Radiation therapy		39	95.1	28	80.0	28	93.3	22	71.0	41	89.1	
Chemotherapy		14	34.1	14	40.0	5	16.7	6	19.4	23	50.0	
Relapse		5	12.2	9	25.7	3	10.0	13	41.9	10	21.7	*0.023*
Relapse free survival, median(months)		30.0 (11-46)		28.0 (4-44)		28.5 (0-46)		24.0 (2-43)		27.5 (4-41)		*0.012*

a NAC : neoadjuvant chemotherapy
b concurrent A/T : concurrent anthracycline and taxane
c sequential A→T : sequential anthracycline followed by taxane
d HER2 directed : Trastuzumab or T-DM1(trastuzumab emtansine) containing regimen
e Others : 6 cycles of AC(Doxorubicin + cyclophosphamide)
f BCS : breast conserving surgery
g pCR: pathologic complete response
h PR: partial response
i NR: no response
j HER2 : human epidermal growth factor receptor 2
k TNBC : triple negative breast cancer

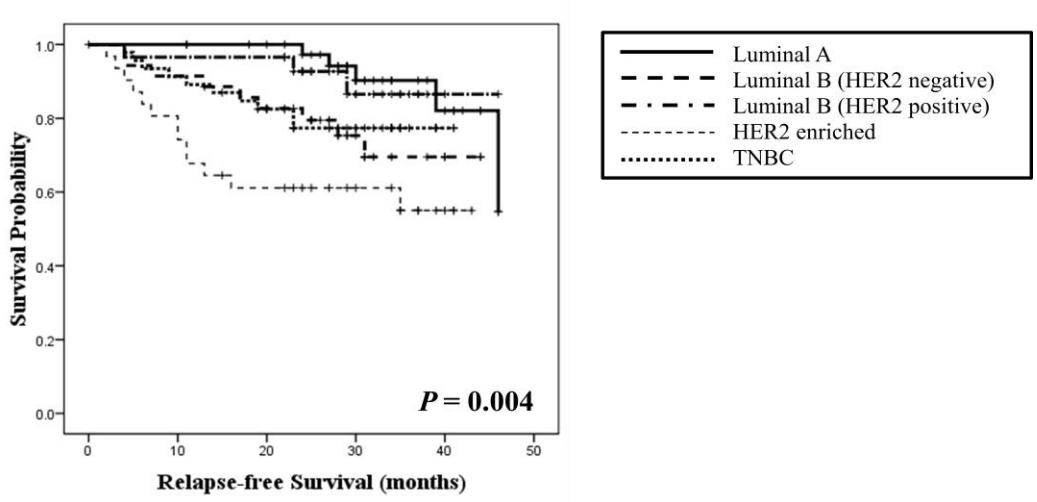
2) Prognostic factors according to Subgroup analysis

Variables	Luminal A			Luminal B			HER2[e]			TNBC[f]		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age												
≤median	0.477	0.078 - 2.907	*0.422*	0.646	0.207 - 2.019	*0.453*	0.616	0.188 - 2.016	*0.423*	0.597	0.168 -2.115	*0.424*
>median	1			1			1			1		
Mennopausal status												
premenopause	0.092	0.009 - 0.906	*0.041*	0.875	0.282 - 2.727	*0.818*	0.482	0.132 - 1.754	*0.268*	0.741	0.214 - 2.558	*0.635*
postmenopause	1			1			1			1		
pCR[a]		-		0.039	0.000 - 46.767	*0.370*	0.360	0.047 - 2.773	*0.327*	0.420	0.053 - 3.323	*0.411*
vs non-pCR				1			1			1		
AJCC response												
pCR	0.128	0.011- 1.493	*0.101*	0.133	0.043 - 0.410	*0.000*	0.295	0.094 - 0.919	*0.035*	0.314	0.106 - 0.935	*0.037*
PR[b] & NR[c]	1			1			1			1		
Pathologic Stage												
yp0,I	0.517	0.247 - 1.081	*0.080*	0.160	0.021 - 1.238	*0.079*	0.162	0.036 - 0.732	*0.018*	0.182	0.038 - 0.861	*0.032*
ypII, III, IV	1			1			1			1		
Surgery												
BCS[d]	0.414	0.069 - 2.493	*0.336*	0.329	0.101 - 1.071	*0.065*	0.296	0.081 - 1.081	*0.065*	0.930	0.240 - 3.660	*0.917*
mastectomy	1			1			1			1		

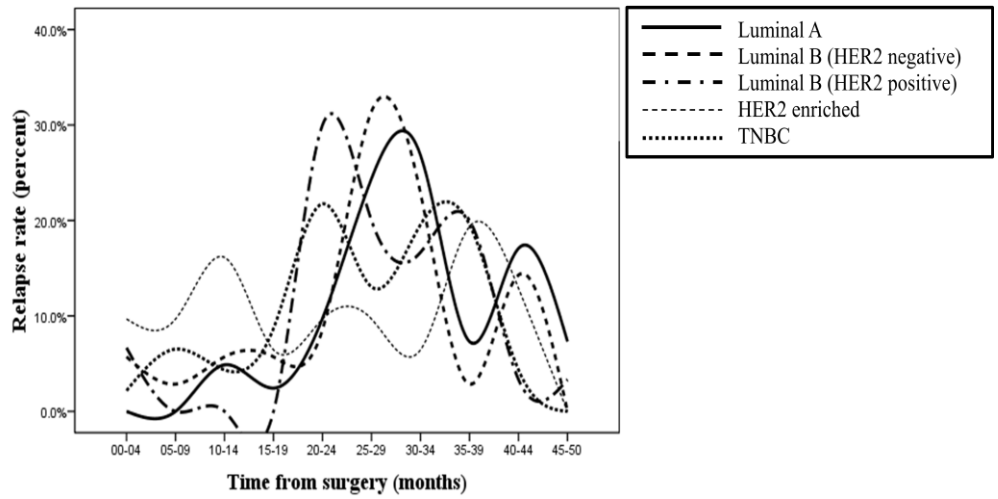
a pCR: pathologic complete response
b PR: partial response
c NR: no response
d BCS : breast conserving surgery
e HER2 : human epidermal growth factor receptor 2
f TNBC : triple negative breast cancer

Figure 5 Breast Cancer Subtypes and Relapse Free Survival

1) RFS according to Breast Cancer Subtypes



2) Relapse Rate and Time from Surgery according to Breast Cancer Subtypes



Clinicopathological prognostic factors for RFS in each breast cancer subgroups were shown in Table 8-2. AJCC response was significantly associated with RFS in all groups except luminal A. Pathologic stage was significantly associated with RFS in HER2 and TNBC group but not in luminal A and luminal B group. Menopausal status was the only clinical factor associated with RFS in luminal A (premonopause vs post-menopause, hazard ratio 0.092, 95% CI 0.009-0.906, *P*=0.041). In multivariate analysis with adjusting age and pathologic stage, premenopause was still positive prognostic factor for the RFS (hazard ratio 0.080, 95% CI 0.007-0.988, P=0.049).

In biomarker analyses (Table 7), all the markers examined were not statistically significant in hormone receptor positive group. In TNBC patients, p53, Bcl-2, EGFR, CK 5/6 did not show association with RFS. The Ki-67 overexpression itself as a binary predictor (cut-off value of 'high' as ≥14%) in both initial and final tissue specimens were not associated with RFS. Ki-67 difference (Ki-67 index final subtracted by Ki-67 index initial) as a continuous variables was not statistically significant, either. We further divided the patients into three groups by categorical change of Ki-67 index with cut-off value of 14%, as high (≥14%) → high, high → low (<14%), low → high/low (Figure 6-1). Categorical change of Ki-67 index from high to

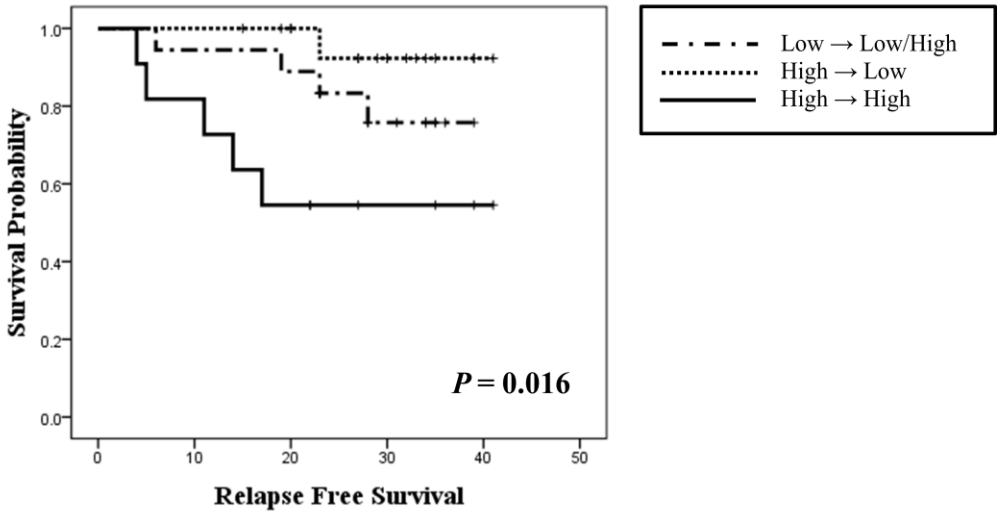
low was significantly associated with longer RFS in TNBC group (Figure 6-2, log rank, *P*=0.016) but not in hormone receptor positive or HER2 positive group.

Figure 6. Ki-67 Index Change and Relapse Free Survival in Triple Negative Breast Cancer

1) Ki-67 Index Change in Triple Negative Breast Cancer Patients

Ki-67 index		Number or patients (percent)	
Initial	**Post-neoadjuvant chemotherapy**	**Total**	**Relapse** Number (percent)
Low	**Low/High**	18	4 (25%)
High	**Low**	17	1 (5.9%)
High	**High**	11	5 (45.5%)
overall		46	10 (21.7%)

2) Ki-67 Index Change and Relapse Free Survival in Triple Negative Breast Cancer



Discussion

Response to the neoadjuvant chemotherapy in stage II or stage III breast cancer has a prognostic impact on relapse free survival and overall survival. [8, 48] [49] Pathologic CR (pCR) is an alleged surrogate marker for the response to NAC. Addition of preoperative taxanes to doxorubicin and cyclophosphamide (AC) increased the proportion of patients having pathologic pCR compared with preoperative AC alone (26% vs 13%, respectively; $P < 0.001$). [50] After the result of NSABP B-27 together with B-18 and several studies, the long course of NAC to achieve higher pCR became more popular in clinical practice. [15, 16, 50] Previous study of Keam et al. showed that AJCC response criteria for NAC correlates well with radiologic response criteria and has a prognostic value for both relapse free survival and overall survival in patients with short course of NAC (three cycles of concurrent doxorubicin plus docetaxel chemotherapy). Complete response, PR and NR rate were 9.8, 59.3, and 30.7% respectively. The 5-year RFS rates were 89.6, 74.1, 62.6% (P=0.002) and the 5-year OS rates were 97.4, 88.6 and 78.3% (P=0.012) in CR, PR and NR group respectively. [14] In current study, we demonstrated AJCC response criteria is still a useful prognostic factor for the RFS in patients with long course (≥ 6 cycles of) NAC. The rate of CR, PR is significantly higher (12% and 67.2%

respectively) than the short course NAC in previous study. Since the follow up duration is short, the prognostic impact of AJCC response with long course NAC on overall survival was not obtained.

Previous studies showed the different rates or pCR between breast cancer subgroups [51] and thus the clinical usefulness of pCR as a surrogate marker for survival is different between the groups. According to von Minckwitz et al, pCR is a suitable surrogate end point for patients with luminal B/HER2-negative, HER2-positive (nonluminal), and triple-negative disease but not for those with luminal B/HER2-positive or luminal A tumors. [48] In our analyses for the four breast cancer subgroups, AJCC response criteria was a significant prognostic marker for RFS in all the groups except for the luminal A (LA). Because LA type is a slowly proliferating tumor, response to the NAC is not as good as in highly proliferating tumor types and AJCC response would not be associated with prognosis. This result is consistent with the previous reports of prognostic role of pCR in each breast cancer subgroups. [48] But unlike in the previous reports, pCR was not associate with RFS neither in total study population nor in any subgroups of patients in current study. This might be resulted from a short follow up period, result into a lack of sufficient event (relapse) number for obtaining the statistical

power. Further follow up is need for confirm the prognostic impact of AJCC response criteria and pCR in each breast cancer subgroups.

In LA group patients, pCR was not achieved in both short and long course NAC. AJCC response rate (PR and NR portion) and the breast conserving surgery rate were not different in both short and long course NAC groups. (P=0.297 and P=0.174 respectively, not shown in table) From these results, we can suggest that in LA patients, the long course NAC would not be as beneficial as in other aggressive histologic subtypes. And different NAC strategies are needed in different histopatholgic breast cancer subtypes.

From the analyses of relapse rate at the specific time from surgery (Figure 2 and Figure 5-2), we obtained several clinical implications. According to the breast cancer subgroup and the AJCC response to NAC, the peak time of relapse rate is different. For the patients with HER2 positive (nonluminal) and AJCC NR group, meticulous physical examination and work up for locoregional and/or distant metastases should be performed even during adjuvant therapies. And from these data, we could obtain the background for further adjuvant chemotherapy even after the use of both anthracycline and taxane containing long course NAC and could select the high-risk patients who needed adjuvant chemotherapy. Actually, there are two ongoing

adjuvant clinical trials targeting for the high risk patients with residual diseases after neoadjuvant chemotherapy. (JBCRG04 (CREATE-X), NCT01864746 (PENELOPE-B))

We also analyzed the clinical and pathological prognostic factors for RFS in breast cancer subgroups. In LA group the only clinicopathological factor that is statistically significant for RFS is menopausal status. We found a clue for explanation of this phenomenon at the recent study of Prat et al. [52] and the letter to the same journal by Yamamoto et al. [53] The incidence of ER-positive/PR-negative (or low) tumors is reported to increase after menopause. [54, 55] And some of the PR-low tumors showed low endocrine responsiveness related to ER-independent growth. In premenopausal patient group, ER-positive/PR-negative (or low) portion is low, and the response to the adjuvant hormonal therapy would be better than the post-menopausal patient group. In HER2 and TNBC group, pathologic stage of tumor was significantly related to RFS.

In pathological biomarker analysis, hormone receptor positivity and the bcl-2 positivity is positively associated with RFS in the total study patients. The bcl-2 immunoreactivity is known to be related to hormone receptor positivity and more prevalent in well-differentiated tumors. [56] So the bcl-2 positivity

itself might not be the independent prognostic factor for survival. Actually after adjusting hormone receptor status, bcl-2 is not significantly associated with RFS. Ki-67 is a cell proliferation-associated antigen which is the simplest and the most widely used method to assess tumor proliferation. [57, 58] Several studies already showed the predictive and the prognostic value of Ki-67 index in the stage II/III breast cancer with NAC setting. [38, 39, 43, 47, 59-61] In previous study of our hospital demonstrated that higher Ki-67 index was associated with a more aggressive clinical feature despite a higher response to NAC in the TNBC patient group. [39] In current study, we analyzed Ki-67 (both pre- and post-NAC) as a binary predictor with cut off value of 14%, Ki-67 (post-NAC) as a continuous variable and Ki-67 difference (pre-NAC Ki-67 subtracted by post-NAC Ki-67) as a continuous variable. None were associated with RFS, and their relationship with OS was not obtained during the study period. We also analyzed RFS with a three-category model (high (≥14%) → high, high → low (<14%), low → high/low) according to the change of Ki-67 index. The categorical change of the Ki-67 index was associated with RFS in TNBC group. As in the previous reports, we confirm the clinical usefulness of Ki-67 index in TNBC patients in NAC setting but the accurate model for the survival predication was not identified in this study. Further long term follow up is needed for confirming the

clinical impact of Ki-67 index (both for the pre- and post-Ki-67 index itself and for the Ki-67 indices change).

Our study included some limitations. First, as for the retrospective design of the study, the probability of selection bias of selected patients with good response to NAC (whose cancer did not progressed during the NAC) and excluded the patients with early progression or non-response is existed. The patients with short course (< 6cycles) of NAC in the same period (total number of 66) consisted of the patients whom initially planned to receive short course of chemotherapy and the ones progressed during NAC. There were limitations to distinguish the two groups by retrospective medical record review. Per medical record review, there was only one patient with definite clinical disease progression during NAC, who received mastectomy after 3 cycles of NAC. And by the radiologic response criteria, there were no difference in the portion of patients with progressive disease (4.5% vs 4.4%, <6 cycles vs ≥6 cycles of NAC respectively, shown in Table 5). So the selection bias expected to be minimal in this study. Second, the follow up duration is short, so the prognostic impact of AJCC response criteria for overall survival in long course of NAC could not be demonstrated in this study.

Despite these limitations, this is the first report demonstrated clinical usefulness of AJCC response criteria in the patients with 6 or more cycles of NAC with neoadjuvant chemotherapy regimens used in clinical practice. AJCC criteria is a simple, eidetic and easily reproducible tool for response evaluation for breast cancer patients in NAC setting compared with classically used residual cancer burden (RCB) measurement method or Miller-Payne grading system. [9] [11] Furthermore we performed pre-and post-NAC paired imaging study (Breast MRI or chest CT with breast ultrasonography) for the clinical staging and examination for radiologic response evaluation. And we also had pre-and post-NAC paired tissue for pathological examination and evaluating the potential prognostic role of biomarkers. Further follow-up is needed to establish the potential prognostic role of AJCC and other clincopathological markers for the overall survival.

Conclusion

AJCC criteria is a simple, eidetic and easily reproducible clinical marker for predicting RFS in the patients with stage II/III breast cancer, who received long course of neoadjuvant chemotherapy. Further long term follow-up is needed to determine the prognostic role of AJCC response criteria for the overall survival.

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국문초록

6주기 이상 장기간 선행항암요법을 받은 유방암 환자에서 American Joint Committee on Cancer (AJCC) 반응평가 기준의 임상적 유용성

서론

진단 시 American Joint Committee on Cancer (AJCC) 병기 II기 및 III기 유방암에서 수술 전 선행화학요법은 현재 표준치료로 자리 잡았다. 선행화학요법에 대한 AJCC 반응평가 기준은 3주기의 단기간 선행항암화학요법을 시행한 환자군에서 반응평가의 유용한 도구인 동시에 재발 없는 생존기간 및 전체생존기간의 예측할 수 있는 인자로 알려져 있다. 이번 연구를 통해서 6주기 이상의 연장된 선행화학요법을 시행한 환자군에서도 AJCC 반응평가기준이 여전히 임상적 유용성을 가지는지에 대해 밝히고자 한다. 아울러 유방암환자를 분자생물학적 특징을 바탕으로 4개의 군으로 나누었을 때 각 군에서의 AJCC 반응평가기준의 유용성 및 임상적, 병리학적 예후예측인자를 분석하였다.

방법

2009년 1월부터 2010년 12월까지의 기간 동안 유방암의 임상적 병기 II기 및 III기였던 환자 중 6주기 이상의 연장된 선행화학요법을 받은 환자 183명이 이 연구에 포함되었다. 유방암 선행화학요법 후 AJCC 반응 및 임상적, 조직학적 요인들에 대해서 후향적으로 분석하였다. 이 논문에서 사용한 AJCC 반응평가기준은 다음과 같이 세 군으로 분류된다. (1) 완전반응 – 유방조직 및 림프절에 모두 침윤성 암이 없는 경우, (2) 부분반응 – 선행화학요법 후 처음에 비해 T 혹은 N 병기의 감소가 있는 경우, (3) 반응없음 – 선행화학요법 전후로 T와 N 병기 모두 차이가 없거나 둘 중 하나라도 증가한 경우로 정의된다.

결과

6주기 이상의 연장된 선행화학요법을 받은 국소진행성 유방암 183명의 환자들을 중앙추적기간 38.0개월 동안 관찰하였다. AJCC 반응평가기준에 따라 완전반응, 부분반응, 반응없음은 각각 22명 (12.0%), 123명 (67.2%) 그리고 38명 (20.8%)을 차지하였다. 3년

간의 재발 없는 생존율은 세 군에서 각각 90.9%, 80.8% 그리고 48.5%의 결과를 보였다. Cox 회귀분석을 시행하였을 때 AJCC 반응평가기준은 통계적으로 유의하게 재발 없는 생존기간과 연관성을 보였다. ($P<0.001$) 잠재적인 예후예측인자를 보정한 후에도 AJCC 반응평가기준은 독립적으로 유의하게 재발 없는 생존기간과 연관이 있었다. (P=0.004)

결론

국소진행성 유방암에서 6주기이상의 연장된 선행화학요법을 시행하는 경우에 AJCC 반응평가기준은 통계적으로 유의한 재발 없는 생존기간의 예후인자이다.

주요어

임상적 병기 II/III 기 유방암, 선행화학요법, AJCC 반응평가기준, 재발 없는 생존기간

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